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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,650	GOINS ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 29-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 29-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1 and 15 have been amended, and claims 29-38 have been added by the amendment filed May 12, 2004.

Claims 1-19, 29-38 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 29-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising:

a) injecting into a mammal a first composition comprising a ligand complexed to a colloidal particle having the diameter of less than 500 nm; and

b) injecting to said mammal a second composition comprising an anti-ligand which binds to said ligand,

wherein an active agent is conjugated to either said colloid or said anti-ligand,

and whereby the anti-ligand encounters and causes aggregation of the colloid-ligand complex at, or just prior to reaching, the one or more targeted lymph nodes; and

A method for detecting one ore more sentinel lymph nodes, comprising:

a) injecting into a mammal a first composition comprising a ligand complexed to a colloidal particle having the diameter of less than 500 nm; and

b) injecting to said mammal a second composition comprising an anti-ligand which binds to said ligand,

wherein an active agent chosen from a radioisotope or dye is conjugated to either said colloid or said anti-ligand,

whereby the anti-ligand encounters and causes aggregation of the colloid-ligand complex at, or just prior to reaching, the one or more sentinel lymph nodes, and whereby said sentinel lymph nodes are detectable.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The main thrust of the invention is the concept of injecting two compositions to a mammal in order to target the delivery of any known bioactive agent to lymph nodes, wherein the first injected composition comprises a colloid particle coated with a ligand, *e.g.,* biotin, and wherein the second injected composition comprises an anti-ligand, *e.g.,* avidin. The state of the art of targeted delivery to lymph nodes by using a generic colloid-base system is not conventional and routine at the time the invention was made, see the references cited in the second full par. on page 6 of the specification, Moghimi, Prog, Biophys. Molec. Biol., Vol. 65, 3, pp. 221-249, 1996 (IDS), Oussoren, Biochimica et Biophysica Acta 1328, 261,272, 1997. One of the important issues that were raised

in the cited references including the as-filed specification is the influence of a colloid particle size, its contents. The as-filed specification clearly teaches such on page 13, and specifically states that "if the colloid-ligand composition is too large, it is retained at the site of injection", and that "if the colloid-ligand composition is too small, it is transported from the site of injection into the circulation and is not retained in the lymph nodes". However, the claims as presently pending embrace the use of an enormous number of colloid particles, regardless of their sizes, in order to achieve the targeted delivery of a bioactive agent to lymph nodes for a sufficient amount of time required for the agent's activity. In fact, Oussoren teaches and provides factual evidence (Figure 3A) demonstrating that only smaller liposomes (less than 400 nm in mean size) were able to enter the lymphatic capillaries, and that even with the liposomes with the 400 nm in mean size, roughly more than 80% of the contents remain at the injected site. None of the working examples employs liposomes with mean sizes larger than 500 nm. Thus, given the fact that detailed information on factors influencing lymphatic targeted drug delivery remains unsettled within the those of skill in the art, that the as-filed specification does not provide any solution to the criticality of the colloidal size, and given the reasons set forth, one skilled in the art would not have been able to reasonably extrapolates, from the teachings and/or working examples provided by the specification to the entire breadth of the claimed invention.

Another issue which is essential for the usage within the context of the specification is the teaching provided by the specification on page 15, which clearly teaches that in order for the targeted delivery to the lymph nodes to work, the two

compositions must be injected within a sufficient amount of time and/or at locations, so that the injected anti-ligand would encounter the colloid-ligand at, or just prior to reaching, the targeted lymph node, whereby such encounter would cause aggregation of the colloid-ligand and its subsequent retention at the targeted lymph nodes. As such, the claims are only reasonably enabling for claimed embodiments, wherein such steps are employed in order to have the injected anti-ligand encountering the colloid-ligand at, or just prior to reaching, the targeted lymph node.

With respect to the breadth of presently pending claims, which encompasses numerous ligands and anti-ligands other than biotin and avidin, and colloid based systems other than liposomes, Philips WT, (abstract, July 16, 1999, 9th Annual Smposium on Cancer Research in San Antonio, IDS) teaches:

The avidin injection causes aggregation of the biotin coated liposomes that are in the process of migrating through lymphatic vessels. When this aggregated liposome complex reaches the next encountered lymph node, it becomes retained for a prolonged time in this node. This prolonged retention contrasts greatly with control liposome preparations which simply pass through the lymph node without retention.

The specification on pages 23 and 24 acknowledges the same as indicated above by Philips WT.

Thus, it is apparent to one skill in the art, particularly on the basis of the teaching provided by the specification and the state of the art exemplified by Philips, that the aggregation property caused by the injected anti-ligand is essential for the targeted delivery and retention a colloidal delivery system as claimed. Thus, the presently

pending claims are only reasonably enabling for such claimed embodiments, wherein a combination of a colloidal particle (such as nanoparticles, microparticles, microcapsules, dendrimers, lipid based particles) with a size range of less than 500 nm, and of ligan/anti-ligand, all of which exhibit the property of being able to conjugate and to cause aggregation of the injected complexes prior to their entry into the targeted lymph nodes through the lymphatic system.

In view of reasons set forth above, it would require an undue experimentation for one skilled in the art to practice the full breadth of the claimed invention at the time the invention was made.

Applicant's response (dated May 12, 2004) has been considered by the examiner but is not found persuasive because of the reasons set forth in the stated rejection and because of the following reasons:

Applicant asserts on page 7 bridging page 8 that the rejection is improper, however, the rejection does satisfactorily shows with sufficient evidence that the full breadth of the claimed invention was not reasonably enabled at the time the invention was made. Other than the level of a person skilled in the art, which is relatively high at the time the invention was made, the examiner has considered fully the guidance, the state of the prior art, the working examples, the breadth of the claims, and the nature of the invention, and thus, has found insufficient envidence from the as-filed application to fully enable a person skilled in the art to make and use the full scope of the claimed subject matter at the time the invention was made.

On page 8 bridging page 9, Applicant has cited MPEP & numerous court decisions such as MPEP 2164.04, *United States v Telectronics, Inc, Johns Hopkins Univ. V CellPro, Inc.* to support applicant's position. More specifically, applicant asserts that a composition claim is not limited by a recited used, and that any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on that use. However, none of presently pending claims is directed to either a product or composition claim. As such and insofar as the claimed methods are directed to a specific use such as an intended use of a targeted delivery of any biologically active agent including those of therapeutic DNA to one or more lymph nodes, wherein a genus of colloids is embraced and wherein the biologically active agent is not even recited in the claims, the stated rejection has provide ample evidence showing that the claimed invention is not reasonably enabled in its full breadth at the time the invention was made. Thus, the citations of MPEP and court decisions are not found to be relevant to the specific issues as set forth in the stated rejection, and thus, are found unpersuasive.

Applicant further asserts on page 9 that the "how to make" issue is not raised in the office action. The response is found partially correct. To the extent that "how to make" is relevant to the "how to use" the as-filed application plus applicant's latest response as a whole does not provide any specific evidence to rebut the specific issues as set forth in the stated rejection. More to a point, the as-filed specification clearly teaches such on page 13, and specifically states that "if the colloid-ligand composition is too large, it is retained at the site of injection", and that "if the colloid-ligand composition

is too small, it is transported from the site of injection into the circulation and is not retained in the lymph nodes". However, the claims as presently pending embrace the use of an enormous number of colloid particles, regardless of their sizes, in order to achieve the targeted delivery of a bioactive agent to lymph nodes for a sufficient amount of time required for the agent's activity. In fact, Oussoren teaches and provides factual evidence (Figure 3A) demonstrating that only smaller liposomes (less than 400 nm in mean size) were able to enter the lymphatic capillaries, and that even with the liposomes with the 400 nm in mean size, roughly more than 80% of the contents remain at the injected site. None of the working examples employs liposomes with mean sizes larger than 500 nm. Thus, given the fact that detailed information on factors influencing lymphatic targeted drug delivery remains unsettled within the those of skill in the art, that the as-filed specification does not provide any solution to the criticality of the colloidal size, and given the reasons set forth, one skilled in the art would not have been able to reasonably extrapolates, from the teachings and/or working examples provided by the specification to the entire breadth of the claimed invention.

Another issue which is essential for the usage within the context of the specification is the teaching provided by the specification on page 15, which clearly teaches that in order for the targeted delivery to the lymph nodes to work, the two compositions must be injected within a sufficient amount of time and/or at locations, so that the injected anti-ligand would encounter the colloid-ligand at, or just prior to reaching, the targeted lymph node, whereby such encounter would cause aggregation of the colloid-ligand and its subsequent retention at the targeted lymph nodes. As such,

the claims are only reasonably enabling for claimed emobodiments, wherein such steps are employed in order to have the injected anti-ligand encountering the colloid-ligand at, or just prior to reaching, the targeted lymph node.

With respect to the breadth of presently pending claims, which encompasses numerous ligands and anti-ligands other than biotin and avidin, and colloid based systems other than liposomes, Philips WT, (abstract, July 16, 1999, 9th Annual Smposium on Cancer Research in San Antonio, IDS) teaches:

The avidin injection causes aggregation of the biotin coated liposomes that are in the process of migrating through lymphatic vessels. When this aggregated liposome complex reaches the next encountered lymph node, it becomes retained for a prolonged time in this node. This prolonged retention contrasts greatly with control liposome preparations which simply pass through the lymph node without retention.

The specification on pages 23 and 24 acknowledges the same as indicated above by Philips WT.

Thus, it is apparent to one skill in the art, particularly on the basis of the teaching provided by the specification and the state of the art exemplified by Philips, that the aggregation property caused by the injected anti-ligand is essential for the targeted delivery and retention a colloidal delivery system as claimed. Thus, the presently pending claims are only reasonably enabling for such claimed embodiments, wherein a combination of a colloidal particle (such as nanoparticles, microparticles, microcapsules, dendrimers, lipid based particles) with a size range of less than 500 nm, and of ligan/anti-ligand, all of which exhibit the property of being able to conjugate and to

cause aggregation of the injected complexes prior to their entry into the targeted lymph nodes through the lymphatic system.

The examiner further notes that none of the working examples as relied upon by applicants is directed to the issues as set forth in the immediately preceding paragraphs. The examiner also notes that the issue is not the total lack of enablement of the claimed subject matters, but rather is whether or not applicant is entitled to claim broadly as that in the base claims. The examiner has provided suggestions on record showing that should applicant claim a method for delivery and retention of an active agent in one or more targeted lymph nodes, comprising:

a) injecting into a mammal a first composition comprising a ligand complexed to a colloidal particle having the diameter of less than 500 nm; and

b) injecting to said mammal a second composition comprising an anti-ligand which binds to said ligand,

wherein an active agent is conjugated to either said colloid or said anti-ligand,

and whereby the anti-ligand encounters and causes aggregation of the colloid-ligand complex at, or just prior to reaching, the one or more targeted lymph nodes,

the stated rejection would be withdrawn by the examiner.

Should applicant believe that applicant's claims should be entitled to be claim broadly as that in the presently pending claims, applicant is invited to provide more specific evidence to rebut the specific issues as set forth in the stated rejection. Simple citations of court decisions, MPEP(s), or even applicant's work without providing

sufficient evidence to overcome the specifically raised issues in the stated rejection are not deemed persuasive in order to overcome the stated rejection.

Applicant asserts on page 10 that by simply by simply claiming an intended use or end point of the claimed methods, such claimed language is evidence that the colloidal particle size must be of a sufficient size to be delivered and retained in the targeted lymph node or to detect a sentinel lymph node. Applicant's assertion appears to be a conclusory statement and is not sufficient *per se* to overcome the broadly claimed subject matter. Applicant asserts of a "sufficient size", however, neither the as-filed application nor the claims disclose as to what are exactly the meanings of such "sufficient size". To the extent that a broadest reasonable interpretation can be applied to the claims, it is apparent that applicant contemplates any colloid of an undefined "sufficient size" that could achieve the end point of the claimed methods. However, the state of the prior art, the reasoning as set forth in the stated rejection, and the as-filed specification do not support applicant's position that no undue experimentation is required to determine colloids of a "sufficient size" as embraced by the claims. Applicant's argument without any factual evidence appears to further support the non-enablement of the full breadth of claims. Thus, the citations of *In re Fisher* and MPEP 2164.01 are also not found persuasive. Applicant further asserts on page 11 that the issue of "where the ligand/antiligand aggregation occurs prior to their entry into the targeted lymph odes is raised without any merit. The examiner has revisited the issue and has found that the issue is raised with merit. Thus and to the extent that the claims

have not been amended to reflect the given enabling breadth, the stated rejection is reasonable, proper, and thus, is maintained.

Applicant 's assertion as to the improperness of the prior art rejection of claims 20-28 is moot since the claims have been canceled. For the record, the examiner has not considered such assertion.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19, 29-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the base claims, the newly added term "the lymph node" does not contain a proper antecedent basis. While the body of the base claims recite "one more targeted lymph nodes" or "one or more sentinel lymph nodes", it is not apparent as to what is exact a lymph node among the previously recited "lymph nodes" or "sentinel lymph nodes", the term "the lymph node" refers to.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 29, and 31-34 are rejected under 35 USC 103 as being unpatentable over Allen taken with either Griffiths or Gustavson (US Pat No. 5,420,105), and further in view of Oussoren (Biochimica et Biophysica, 1328, 261272, 1997, IDS).

Allen teaches a method of delivering a first composition comprising a ligand conjugated to a tumor specific antibody to a mammal, and delivering to the mammal another composition comprising an anti-ligand/therapeutic agent/diagnostic agent containing liposomal carriers, wherein the liposomal carriers having the sizes predominantly in the range 0.05 to 0.12 microns (abstract, column 6, lines 44-59, column 7 bridging column 8, column 9, lines 29-36, column 10, lines 17-27, column 12, and column 20). Specifically, the ligand/anti-ligand binding pair is biotin and avidin, or avidin and biotin, respectively. Column 12, for example, discloses that the first delivered composition comprises a ligand, biotin, for example, conjugated to a tumor specific antibody as an active agent. The antibody is specific to a tumor associated antigen, and thus, is expected by a skilled artisan to target only tumor cells rather than healthy cells. Column 12 also discloses that a second delivered composition comprises an anti-ligand (avidin) conjugated to a therapeutic agent/diagnostic agent entrapped liposome. The liposome of Allen is preferably a derivatized vesicle-forming lipid, which includes DSPC (PC based lipid coated with a polymer such as PEG, column 5). Means of employing the compositions for imaging or therapeutic application are disclosed throughout the reference, especially column 11, lines 32-61. Allen specifically teaches that the liposomal composition is utilized specifically for tumor treatment, especially blood-born tumors (column 11, last full par), and that by having a lipid particle or

lipid/hydrophilic polymer particles, the antibody and therapeutic agents are expected to circulate in the bloodstream over an extended period of time (column 3, lines 30-38). The active agent can also include a radioisotope as an imaging agent (column 12, last par.). Since non-direct administrations are employed for both the biotin and avidin's conjugates, and since tumor cells are freely floating in the bloodstream, one of ordinary skill in the art would have reasonably expected that the antibodies conjugated to biotin would bind to a targeted tumor associated antigen, and thus, would bind specifically to the avidin at the freely floated tumor cells in the bloodstream. Allen does teach that

Allen does not teach explicitly that the liposomal particle can also be used to enhance the delivery of the first composition comprising a tumor specific antibody conjugated to a ligand such as biotin to one ore more targeted lymph nodes and that an anti-ligand/therapeutic compound/liposomal complex is administered separately, whereby the biotin binds to avidin prior to their entry into the one or more targeted lymph nodes, nor does Allen teach that a dye can be used to enhance the visualization of the delivered agents in a treated subject.

However, both Griffiths and Gustavson teach that a colloidal based system such as a biocompatible polymeric carrier containing a biotin or avidin is effective to increase the targeting of both a ligand conjugate or a subsequent anti-ligand conjugate at an intended target site such as a tumor site (Griffiths, abstract, column 7, lines 32-36, column 8; Gustavson, column 3, column 14, lines 8-15).

It would have been obvious for one of ordinary skill in the art to employ a colloidal based delivery carrier to enhance the delivery and binding of ligand/anti-ligand at a

target tumor cell to which the first delivered ligand is bound in the bloodstream. One of ordinary skill in the art would have been motivated to employ any known colloidal based delivery carrier in the ligand conjugate of Allen. One of ordinary skill in the art would have been motivated to employ a colloidal particle such as those described in Griffiths or Gustavson because such incorporation of the particle to a ligand and/or anti-ligand would not only enhance the delivery and stability of the antibody during its traversal to an intended target tumor site, but also provides an increased number of binding sites to which a subsequently administered composition such as the avidin/therapeutic agent/imaging agent/liposome can bind, thereby amplifying the amount of detection or therapeutic agent at the targeted tumor cells in a blood-born tumor or metastasized tumor. Note that Allen teaches throughout the reference that biotin/antibody conjugates bound to lipid particles or lipid/polymer particles circulate in the bloodstream over an extended period of time relative to those not bound to colloidal particles.

Because of the fact that the combined cited references teach that a colloidal particle is suitable carrier for use in systemic administration and/or pareteral administraton of the claimed composition, it would also have been obvious to a ordinary skilled artisan that any other typically used administration route as employed in art of drug delivery would be a minor modification and thus a matter of equivalent and design choice, particularly in the absence of any unexpected result.

In the event that one of ordinary skill in the art would employ the delivered composition to target blood born tumor sites such as leukemia by any typical route of administration such as those disclosed in the newly added claims, wherein metastases

are already formulated (as taught by Allen), *e.g.*, invasions of tumors in the lymphatic system, as evidenced by numerous prior art cited in the IDS, one would have reasonably expected that the liposomal composition of Allen is localized and retained at any tumor site in a leukemia patient such as those residing in lymph nodes because of the evidences and teachings provided by Oussoren, which clearly teaches that colloidal particles up to about .4 um in diameter are transported from an injection site into the lymphatic capillaries and localized in regional lymph nodes (Figure 3). As such, and given that the materials and methods steps employed by the combined cited references are identical to that of the claims, and that the as-filed specification specifically supports such steps and materials in order to achieve the functional limitations as recited in the claims, the cancer treatment methods, as taught by the combined cited references, would also result to a binding between an anti-ligand to said ligand prior to entering a lymph node, particularly in the absence of any evidence to the contrary.

It would also have been obvious for one of ordinary skill in the art to employ a radioisotope or an equivalent imaging molecule such as a dye as an imaging detector in any of the components employed in a ligand/antibody conjugate or the lipid based carrier in Allen taken with Griffiths or Gustavson. One of ordinary skill in the art would have been motivated to employ a radioisotope in either the antibody conjugated with a colloidal particle or the lipid based carrier because the prior art of record as a whole, exemplified by Allen, teaches that the use of a radioisotope would provide an stabilized imaging agent for visualizing the distribution of the delivered agent at the targeted tumor sites.

Thus, the claimed invention was *prima facie* obvious.

Applicant's response (pages 13-15) has been considered by the examiner but is not found persuasive because of the following reasons:

Mainly applicant asserts that

1) the limitation, which recites a binding between an anti-ligand to said ligand prior to entering the lymph node, is not taught by the combined cited references. However, such is a functional limitation, and to the extent that applicant continues to assert that any colloid with an undefined sufficient size can be used in a targeted delivery of a bioactive agent to a lymph node, and that the steps and materials as employed by the combined cited references are specifically support by the as-filed application as being able to aggregate and provide a binding between an anti-ligand to said ligand prior to entering the lymph node, the methods, as taught by the combined cited references, would also result to a binding between an anti-ligand to said ligand prior to entering the lymph node, particularly in the absence of evidence to the contrary. Applicant argues about "no reasonable expectation of success" and yet, applicant continues to argue that it is routine to employ applicant's broad claimed method to deliver a biologically active agent to one or more lymph nodes. Such contradiction and simple consclusory statements are not sufficient to overcome the prior art rejection. Given

the teachings of the cited references and level of skill in the ordinary skilled artisan at the time of applicant's invention, it must be considered that the ordinary skilled artisan would have a reasonable expectation of success in practicing the claimed invention, which would necessarily result in a binding between an anti-ligand and a corresponding ligan prior to entering a lymph node. Furthermore, Oussoren, which clearly teaches that colloidal particles up to about .4 um in diameter are transported from an injection site into the lymphatic capillaries and localized in regional lymph nodes (Figure 3), would provide evidentiary support showing that colloidal particles such as those employed in the combined cited references are expected to subsequently enter into a lymph node, regardless whether or not the primary reference is silent on the "lymph node" issue. Note that the fact that applicant has recognized another advantage about the "lymph node" targeting function, which would flow naturally from following the suggestion in the prior art cannot be the basis for patentability when the differences would otherwise be obvious, even though the advantage was unknown in the primary reference/secondary references.

2) the limitation of "lymph node" is not even recited by any of the combined cited references, however, insofar as the Allen specifically teaches that the liposomal composition is utilized specifically for tumor treatment, especially blood-born tumors, and to the extent that in blood-born

tumors, tumor cells already trespass, and are entrapped within one or more lymph nodes, as evidenced by the totality of the prior art of record, it is apparent to a person of ordinary skill in the art, that Allen's active agent would be delivered to one or more lymph nodes, particularly in view of the reasons as set forth in 1). In other words, blood-born tumor cells and/or metastasized tumor cells are freely floating in the bloodstream, and thus, an ordinary skilled artisan would have reasonably expected that the biotin-antibody conjugate is binding to avidin entrapped liposome in the bloodstream prior to their final entry into the lymph nodes, regardless whether or not the primary reference's teaching is silent to the final destination of the bound ligan-anti-ligand/liposomal complex, which is one or more targeted lymph nodes.

3) Applicant's argument regarding the limitation of "one or more sentinel lymph nodes" is found persuasive since the method taught by Allen taken with either Griffiths or Gustavson, and further in view of Oussoren does not specifically teach a method of delivering or monitoring a sentinel lymph node, which is a fist sign to tumor spread from a primary tumor, but rather teach a method of targeted delivering an active agent including a radioisotope to metastasized tumor cells, which are naturally entrapped in the lymphatic system.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

DAVE T. NGUYEN
PRIMARY EXAMINER

Dave Nguyen
Primary Examiner
Art Unit: 1632